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| ART UNIT | PAPER NUMBER |
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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/523,886 | Applicant(s) GRDINA ET AL. | |
|---|---|---|---|
| | Examiner Shin-Lin Chen | Art Unit 1633 | |

*-- Th MAILING DATE of this communication appears on the cov r sheet with the correspondenc address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3-31* is/are pending in the application.

4a) Of the above claim(s) *14-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-13 and 23-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicants' amendment filed 2-26-02 has been entered. Claim 2 has been canceled. Claims 1, 8-13, 30 and 31 have been amended. Claims 1 and 3-31 are pending and claims 1, 3-13 and 23-31 are under consideration.

### *Claim Objections*

1. Claim 1 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 30. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See M.E.P.. § 706.03(k). The phrase "reducing the number of metastases" in claim 1 has the same meaning as "inhibiting metastases" in claim 30.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 9 recites the limitation "said derivative of aminoalkylphosphorothioate" in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim. Claim 8 recites

"said phosphorothioate is an aminoalkylphosphorothioate compound" but fails to recite any **derivative** of aminoalkylphosphorothioate.

4. Claim 10 recites the limitation "said derivative of aminoalkylphosphorothioate" in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim. Claim 8 recites "said phosphorothioate is an aminoalkylphosphorothioate compound" but fails to recite any **derivative** of aminoalkylphosphorothioate.

5. Claim 1 recites the limitation "**the** number of metastasis" in line 1. There is insufficient antecedent basis for this limitation in the claim. Changing "**the** number of metastasis" to "number of metastasis" would be remedial.

6. Claims 1, 3-13 and 24-31 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See M.E.P.. § 2172.01. The omitted steps are: whether the phosphorothioate or active metabolite thereof is delivered to targeted site and reduces the number of metastases after administering into the animal (claims 1 and 3-13), what is the correlation of stimulation of angiostatin, stimulation of MnSOD, and the activity of metalloproteinase with reducing the number of metastases by phosphorothioate (claims 24-29), whether the phosphorothioate or active metabolite thereof is delivered to targeted site and inhibits metastases in an animal after administering into said animal (claim 30), and whether the phosphorothioate or active metabolite thereof is delivered to targeted site and prevents metastases in an animal after administering into said animal (claim 31).

Applicants argue that "whether the phosphorothioate or active metabolite thereof reduces the number of metastases after administering into the animal" is a result not a step. This is not found persuasive because the preamble of the claim is to reduce the number of metastases in an animal, the method is incomplete without knowing whether the phosphorothioate reach targeted site and reduce the number of metastases.

7. Claims 1-13 and 23-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "the number of metastases" in claim 1 is vague and renders the claim indefinite. It is unclear whether "the number of metastases" means "the number of cancer cells caused by metastases" or "the number of tumor sites caused by metastases". Claims 3-13 and 23-29 depend on claim 1 but fails to clarify the indefiniteness.

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 3-13 and 23-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting or preventing metastases by administering WR-2721 at a concentration of 50mg/kg to 150mg/kg to an animal, does not reasonably provide

enablement for inhibiting or preventing metastases by administering any phosphorothioate or active metabolite thereof other than WR-2721 as disclosed, or administering WR-2721 at a concentration of 10mg/kg to less than 50mg/kg to an animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 2-13 and 23-29 are directed to a method for reducing the number of metastases in an animal having a primary tumor, such as a sarcoma or a carcinoma, by administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof at a concentration of 10mg/kg to 150mg/kg. Claim 6 specifies the animal is a human. Claim 10 specifies the active derivative is the disulfide form. Claims 12 and 13 specify the route of administration is intravenous, intraperitoneal etc., and the phosphorothioate or active metabolite thereof is formulated into solutions, suspensions, tablets etc, respectively. Claims 25-29 specify further monitoring the ability of the subcytoprotective dose of the phosphorothioate or active metabolite to reduce metastases via measuring the activity of matrix metalloproteinase (MMP), such as MMP-2 or MMP-9, the stimulation of angiostatin, or the stimulation of MnSOD gene expression. Claims 30 and 31 are directed to a method for inhibiting or preventing metastases in an animal having a primary tumor by administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof.

The claims encompass any phosphorothioate compound and its active metabolite including the list of compounds disclosed in the specification (page 13). Phosphorothioate

compound includes any compound that has phosphors and thio-group and the genus of the compounds is very broad. The specification only discloses inhibition of metastases by using WR-2721, i.e. amifostine, at a concentration of 50mg/kg to 150mg/kg. The prior art also only teaches using amifostine and c-myc antisense phosphorothioate oligonucleotide for protection against metastases.

The specification fails to provide adequate guidance and evidence for inhibition and prevention of metastases of various tumors by using any phosphorothioate and active metabolites thereof other than WR-2721. Kanclerz et al., 1988 (exhibit D) "treatment with a single dose of WR-2721 (0.4g/kg) promoted lung metastases but exerted a suppressive effect on lymph node tumors. When the radioprotector was given in fractioned schedules in three different doses (0.05g/kg, 0.1g/kg and 0.2g/kg for 10 consecutive days) a slight enhancement of lung metastases and suppression of extrapulmonary metastases was observed". Kanclerz also reports that misonidazole and SR-2508 promote lung metastases formation (e.g. abstract, p. 313, right column). In addition, Milas et al., 1984 (Int. J. Radiation Oncology Biol. Phys., Vol. 10, pp. 41-48) reports that the degree of tumor radioprotection afforded by WR-2721 varies with the type of tumor and assay endpoint" (e.g. abstract). Therefore, doses and schedules of a compound administered to a subject and the type of tumors are important factors in determining the effect of said compound on metastases. The specification also fails to provide adequate guidance and evidence for the inhibition and prevention of metastases of various types of tumors *in vivo* by using any antisense phosphorothioate oligonucleotide at a concentration of 10mg/kg to

150mg/kg, and fails to provide adequate guidance for the correlation of the intended antisense phosphorothioate oligonucleotide and metastases of a particular tumor. In view of such and the very broad genus of phosphorothioate compounds, it would be unpredictable whether a phosphorothioate compound or active metabolite thereof would inhibit or prevent metastases of various tumors *in vivo* at the time of the invention and requires one skilled in the art undue experimentation to practice over the full scope of the invention claimed.

The specification also fails to provide adequate guidance and evidence for inhibition and prevention of metastases of various tumors *in vivo* by using any phosphorothioate and active metabolites thereof, such as WR-2721, at a concentration of 10mg/kg to less than 50mg/kg. As discussed above, the does of a compound is an important factor in determining the effect of said compound on metastases. Kanclerz et al., 1988, indicates that 400mg/kg is the maximum tolerated does for WR-2721. However, it is unclear whether a single does or multiple doses of 10mg/kg to less than 50mg/kg of WR-2721 would be sufficient to inhibit or prevent metastases of various types of tumor *in vivo*. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

### *Claim Rejections - 35 USC § 103*

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

> such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 3-13, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Milas et al., 1984 (IDS-C51) in view of Kanclerz et al., 1988 (exhibit D).

Claims 1, 3-13, 30 and 31 are directed to a method for reducing the number of metastases in an animal having a primary tumor, such as a sarcoma or a carcinoma, by administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof at a concentration of 10mg/kg to 150mg/kg. Claim 6 specifies the animal is a human. Claim 10 specifies the active derivative is the disulfide form. Claims 12 and 13 specify the route of administration is intravenous, intraperitoneal etc., and the phosphorothioate or active metabolite thereof is formulated into solutions, suspensions, tablets etc, respectively. Claims 30 and 31 are directed to a method for inhibiting or preventing metastases in an animal having a primary tumor

by administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof.

Milas teaches WR-2721 greatly reduces the spontaneous metastases induced by cyclophosphamide (CY) and whole body irradiation (WBI) in mice with fibrosarcoma injected i.v. into said mice. WR-2721 was given intraperitoneal (i.p.) at a dose of 400mg/kg before WBI or CY injection and WR-2721 was capable of significant protection against metastases enhancement induced by CY and WBI by preventing radiation- or CY-caused immuno-suppression.

Milas does not teach using WR-2721 in humans or at a concentration of 10mg/kg to 150mg/kg.

Kanclerz teaches "treatment with a single dose of WR-2721 (0.4g/kg) promoted lung metastases but exerted a suppressive effect on lymph node tumors. When the radioprotector was given in fractioned schedules in three different doses (0.05g/kg, 0.1g/kg and 0.2g/kg for 10 consecutive days) a slight enhancement of lung metastases and suppression of extrapulmonary metastases was observed".

It would have been obvious for one of ordinary skill at the time of the invention to use WR-2721 at a concentration of 10mg/kg to 150mg/kg for inhibiting metastases or prevent metastases because Kanclerz teaches using three different doses 0.05g/kg (50mg/kg), 0.1g/kg (100mg/kg) and 0.2g/kg (200mg/kg) for 10 consecutive days to suppress extrapulmonary metastases. It also would have been obvious to use WR-2721 in humans because it was known

in the art to test the effect of WR-2721 in animal model first and eventually to use WR-2721 in humans when applicable.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to reduces the spontaneous metastases induced by cyclophosphamide (CY) and whole body irradiation (WBI) in mice with fibrosarcoma or to suppress extrapulmonary metastases *in vivo*.

12. Claims 1, 23 and 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Milas et al., 1984 (IDS-C51) in view of Kanclerz et al., 1988 (exhibit D) as applied to claims 1, 3-13, 30 and 31 above, and further in view of Golub, 1998 (US Patent No. 5,837,696) and Antras-Ferry et al., 1997 (IDS-C2).

Claims 1, 23 and 25-29 are directed to a method for reducing the number of metastases in an animal having a primary tumor by administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof, and further comprising monitoring the ability of the subcytoprotective dose of the phosphorothioate or active metabolite to reduce metastases via measuring the activity of matrix metalloproteinase (MMP), such as MMP-2 or MMP-9, or the stimulation of MnSOD gene expression.

The teachings of Milas and Kanclerz are as discussed above.

Milas and Kanclerz do not teach measuring the activity of MMP-2, MMP-9, or MnSOD to monitor the ability of the phosphorothioate or active metabolite thereof.

Golub teaches a method of inhibiting cancer growth, including cellular proliferation, invasiveness, or metastasis, in a mammal by administering to said mammal a cancer-inhibitory amount of a tetracycline compound (e.g. 0.1mg/kg/day to 30mg/kg/day), such as CMT-3, and said tetracycline compound specifically inhibit expression of gelatinase A or gelatinase B (MMP-2 or MMP-9) (column 7, 14). Golub also teaches that MMP expression, especially gelatinase expression, is associated with cancer invasiveness or metastasis, and CMT-3 inhibits the expression of MMP-2 and MMP-9 in cancer cells *in vitro*. Golub suggests the method set forth above can be used as a prophylactic treatment by administering the tetracycline compound to a mammal after detection of a gene product or metabolite associated with predisposition to a cancer (e.g. column 6).

Antras-Ferry teaches that Oltipraz (4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione) (OPZ) is a potent chemoprotective agent against chemical induced carcinogenesis in several animal model and OPZ induces the transcription of the manganese superoxide dismutase (MnSOD) in a dose-dependent manner (e.g. abstract).

It would have been obvious for one of ordinary skill at the time of the invention to monitor the ability of the phosphorothioate to reduce metastasis by measuring the activity of MMP-2 or MMP-9 because Golub teaches that MMP expression, especially gelatinase expression, is associated with cancer invasiveness or metastasis, and suggests detection of MMP gene products for a prophylactic treatment using tetracycline compound. It also would have been obvious for one of ordinary skill at the time of the invention to monitor the ability of the

phosphorothioate to reduce metastasis by measuring the stimulation of MnSOD gene expression because OPZ is a chemoprotective agent and OPZ can induce MnSOD gene expression.

One having ordinary skill at the time of the invention would have been motivated to do so in order to monitor the effectiveness of the phosphorothioate and active metabolite thereof in reducing the number of metastasis in tumor bearing animals by measuring the activity of MMP-2 and MMP-9, and gene expression of MnSOD as taught by Golub and Antras-Ferry with reasonable expectation of success.

13. Claims 1, 23 and 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Milas et al., 1984 (IDS-C51) in view of Kanclerz et al., 1988 (exhibit D) as applied to claims 1, 3-13, 30 and 31 above, and further in view of Gately et al., 1997 (IDS-C13).

Claims 1, 23 and 24 are directed to a method for reducing the number of metastases in an animal having a primary tumor by administering to said animal a subcytoprotective dose of a phosphorothioate or active metabolite thereof, and further comprising monitoring the ability of the subcytoprotective dose of the phosphorothioate or active metabolite to reduce metastases via measuring the level of angiostatin stimulation.

The teachings of Milas and Kanclerz are as discussed above.

Milas and Kanclerz do not teach measuring the stimulation of angiostatin to monitor the ability of the phosphorothioate or active metabolite thereof.

Gately teaches angiostatin inhibits angiogenesis *in vitro* and *in vivo* and suppresses the growth of Lewis lung carcinoma metastases.

It would have been obvious for one of ordinary skill at the time of the invention to measure the stimulation of angiostatin for monitoring the ability of the phosphorothioate or active metabolite thereof because angiostatin was known to suppress lung carcinoma metastasis and the stimulation of angiostatin would indicate the reduction of metastases.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to monitor the effectiveness of the phosphorothioate and active metabolite thereof in reducing the number of metastasis in tumor bearing animals by measuring stimulation of angiostatin with reasonable expectation of success.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.